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Form 1/77

11 JAN 2000

Patents Act 1977

1 Title of invention

1 Please give the title of the invention: ANTI-INFLAMMATORY PHARMACEUTICAL FORMULATIONS

2 Applicant's details

☑ First or only applicant

2a If you are applying as a corporate body please give:

Corporate name: NORTON HEALTHCARE LTD

Country *(and State of incorporation, if appropriate)*:

2b If you are applying as an individual or one of a partnership please give in full:

Surname:

Forenames:

2c In all cases, please give the following details:

Address: ALBERT BASIN
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UK postcode *(if applicable)*: E16 2QJ 61 8822 1007

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5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

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Yes ☐ No ☒ ➡ *go to 6*

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ANTI-INFLAMMATORY PHARMACEUTICAL FORMULATIONS

This invention relates to pharmaceutical formulations of anti-inflammatory drugs, particularly non-steroidal anti-inflammatory drugs (NSAIDs).

These NSAIDs are used for the treatment of inflammatory conditions such as osteoarthritis or rheumatoid arthritis. A side effect of the oral administration of NSAIDs particularly with long term usage, is a liability to ulcerogenic effects. NSAID induced ulcers in the stomach are potentially dangerous because few or no symptoms may be detected until significant damage has been caused. Certain prostaglandins, for example misoprostol have been shown to reduce and even prevent such ulcers.

various patent applications relate to use of misoprostol with immediate release drugs, for example GB-A-2135881 (Farmitalia Carlo Erba), WO91/16896 (G D Searle), or where a gastric resistant coating is put over the NSAID in an attempt to reduce further gastric erosion due to release in the stomach of the NSAID, for example WO91/16895, WO91/16886 (G D Searle).

There is an increasing use of sustained release preparations of NSAID drugs to reduce the number of doses required by the patient each day. Although the theory of such preparations is that the majority of the drug is released in the intestine rather than the stomach, in practice there is a significant occurrence of gastric problems. This may be due to release of small amounts of drug within the stomach.

veral hours, dependent on the pH of the gastrointestinal tract in the immediate vicinity.

The NSAID is preferably but not exclusively one of reasonably low weight per standard dose, that is 200 mg or below. Examples of suitable NSAIDs include tiaprofenic acid, piroxicam, flubiprofen, tenoxicam, meloxicam or similar molecules. Salts or other derivatives of these drugs may be employed in a conventional manner. Most preferably the drug is diclofenac sodium, ketoprofen or indomethacin. Mixtures may be used.

It is possible to produce the particles or beads by conventional means. Techniques that can be used can include coating the drug on a non-pariel core preferably composed of inert sugar or similar substance and then overcoating with the required coating before encapsulation. The following steps may be employed.

i. Preparation of inert core by conventional pan coating method

ii Active coating by using rotary type fluidized bed.

iii Protective coating by using rotary type fluidized bed.

iv Enteric coating by using rotary type fluidized bed.

The procedure disclosed in EP-A-519144 may be used.

Drug delivery using capsules avoids a further compression step as may be necessary during tablet manufacture.

An alternative method is to form beads or particles by co-acervation or alternatively by precipitation from solution as described by Zaniboni, Fell and Collett, (Int.J.Pharm, 1995, 125, 151-5).

The coating for the beads may include cellulose derivatives eg hydroxypropyl methyl cellulose, methacrylic acid and derivatives eg methyl methacrylates for example, Eudragrit® (Rhom Pharm), especially Eudragrit L or S. Other standard enteric coating materials may be used for example phthalates, eg cellulose acetate phthalate or preferably hydroxypropylacetate phthalate or polyvinylacetate phthalate. Mixtures of these and other materials may be used to produce delay release coated beads. Normally the coating will include plasticisers eg polyethylene glycol, triacetin or phthalate esters.

The prostaglandin component preferably contains misoprostol optionally together with one or more inert excipients. The prostaglandin is normally provided as a 1:10 or 1:100 dilution on an inert cellulose or other binder or filler. Especially useful material for this invention is hydroxypropyl methyl cellulose. The dosage of prostaglandin may be chosen to be suitable to prevent or reduce stomach ulceration caused by the NSAID. A suitable dose of misoprostol is between 10 - 50 μg preferably 50 - 200 μg per dosage form but this may be increased or decreased depending on the NSAID used.

Preferred dosage forms comprise capsules, preferably hard gelatin capsules.

Tablets where the prostaglandin is mixed with one or more binding agents may be bi-layer tablets wherein the NSAID is formed into a first layer and the prostaglandin is then compressed onto it. A tri-layer tablet with an inert intermediate barrier layer between the NSAID and prostaglandin layers may be employed.

The beads were prepared by spray coating a suspension or solution of ketoprofen onto a non-pareil sugarcore, together with a binder dg polyvinylpyrollidone or hydroxypropylmethyl cellulose. The beads were subsequently coated with a delay release coating eg methylmethacrylate (eg Eudragit (Trade Mark)). Mixtures of beads with various levels of coating were used to give the required therapeutic release pattern.

In a fluidized bed apparatus, uniform spherical inert sugar sphere cores were coated with a first layer consisting of the compounds, an inert water soluble polymer such as hydroxy-propylmethylcellulose or hydroxypropylcellulose, and talc. The second layer consisted of an inert water soluble polymer such as hydroxypropylmethylcellulose or hydroxypropylcellulose, talc and a pigment such as titanium dioxide. The third and enteric coating layer consisted of an enteric coating polymer such as co-polymerized methacrylic acid/methacrylic acid methyl esters, a plasticiser such as triethy acetate or similar plasticisers, and talc.

The layers were applied by conventional fluidized bed coating techniques using aqueous solutions or dispersions.

Pseudo zero release was obtained by use of a mixture of beads released at various pHs or at various times dependent on the type of coating.

The beads in Example 1 contained 40% ketoprofen giving a dose per capsule of 100 mg plus 100 μg misoprostol.

The mix was then filled into suitable hard gelatine capsules.

Beads containing 35% diclofenac sodium ie 75 mg drug per dose were prepared.

The beads were formed as previously described, or by mixing with a bulking agent eg microcrystalline cellulose, moistening with water, extruding and spheronising to give spherical or ovoid particles about 0.5 mm to 1.5 mm in diameter. These were dried and coated as previously described using a standard coating agent. The beads were mixed as required to give the required release profile.

The beads are usually provided with a coating to prevent immediate release in the stomach, particularly release before the misoprostol has dissolved.

SOLUBILITY/%		
Time in alkaline buffer	Example 4 tablets	Arthrotec tablets
30 sec	1.6 - 5.0	0 - 0.5
5 min	11 - 13	1.3 - 3.1
30 min	51 - 60	61 - 71
60 min	86 - 90	74 - 96

9. A dosage form as claimed in claim 2, comprising a mixture of particles, beads or granules with different levels or types of coating.

10. A dosage form as claimed in claim 1, wherein the NSAID is selected from the group consisting of tiaprofenic acid, piroxicam, flubiprofen, tenoxicam, meloxicam and salts and derivatives thereof.

11. A dosage from as claimed in claim 10, wherein the NSAID is selected from the group consisting of diclofenac sodium, ketoprofen and indomethacin and mixtures thereof.

12. A dosage form as claimed in claim 6, wherein the dosage of misoprostol is 50 to 200 μg per dosage form.

13. A dosage form as claimed in claim 2, wherein the particles or beads comprise coatings including the drug on non-pareil cores.

14. A dosage form as claimed in claim 2, wherein the particles or beads are made by co-acervation or precipitation from solution.

15. A dosage form as claimed in claim 13, wherein the beads are made by spheronisation or rotogranulation.

16. A dosage from as claimed in claim 13, wherein the coating includes the drug and an excipient selected from the group consisting of: polyvinyl pyrrolidone, sugars and cellulose derivatives.

ABSTRACT

An oral pharmaceutical dosage form including a mixture of a delay release formulation of a non-steroidal anti-inflammatory drug (NSAID) and a mixture containing a prostaglandin and one or more excipients.